

REMARKS

By this Second Preliminary Amendment, Applicants are now presenting additional new claims 234-258, and are cancelling claims 225 and 226 which were previously submitted with their June 7, 1995 Preliminary Amendment filed with the continuation papers for this application. Thus, with the entry of the amendments above, claims 204-224 and 227-258 will be presented for examination.

The specification has been amended in a number of instances as follows. **First**, Applicants have substituted a new title of the invention that is believed to be more descriptive of the subject matter now embraced by all of the claims, including the phosphate-moiety labeled nucleotide, and the oligo- or polynucleotide, and other compositions comprising such phosphate-moiety labeled nucleotides. **Second**, Applicants have updated the citations for various patents and patent applications referenced in the specification. These citations occur in the first two pages of the specification. It is believed that the updated citations will serve to enhance the readability of the present disclosure by alerting future readers and examiners to the patent numbers cited and incorporated by reference therein. In connection with the updated citations, Applicants note that two patents have already issued in the family to which the instant application belongs. The first, U.S. Patent No. 5,328,824, issued on August 31, 1993 for "Base Moiety Labeled Detectable Nucleotide," and the second, U.S. Patent No. 5,260,433, issued on November 9, 1993 for "Saccharide Specific Binding System Labeled Nucleotides." Copies of the foregoing '824 and '433 patents are attached to this paper as Exhibits 2 and 3, respectively. In addition, a copy of U.S. Patent No. 5,449,767 that issued on September 12, 1995 is attached as Exhibit 4. The '767 patent is incorporated by reference in the instant specification on page 52, lines 20 and 21 (as amended above). **Third**, a minor misspelling on page 103 (lymphokines) has been corrected. **Finally**, a new abstract of the disclosure (attached as Exhibit 1) has been substituted on page 141. It is believed that no new matter has been inserted by any of the foregoing amendments to the specification.

The claims have also been changed as follows. **First**, claims 225 and 226, which were added by Applicants' June 7, 1995 Preliminary Amendment, have been cancelled. **Second**, new claims 234-258 have been added in order to pursue subject matter wherein the phosphate-moiety

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labeled nucleotide has been incorporated in an oligo- or polynucleotide, or other composition. Thus, claims 204 and 234 are generic and independent, being directed to the phosphate-moiety labeled nucleotide, and an oligo- or polynucleotide comprising at least one such phosphate-moiety labeled nucleotide, respectively. By and large, new claims 234-258 correspond to the claims presented in Applicants' June 7, 1995 Preliminary Amendment as follows:

<u>New Claims (Above)</u>	<u>Corresponding Claims</u>	<u>Changes/Comments</u>
<u>SN 08/479,997</u>	<u>SN 08/046,004</u>	
234	204	recites deoxyribonucleotide
235	204	recites ribonucleotide
236	204	recites oligo- or polynucleotide
237	205	same as claim 236 above
238	206	ibid.
239	225 (cancelled)	
240	226 (cancelled)	
241	207	same as claim 236 above
242	208	ibid.
243	209	ibid.
244	210	ibid.
245	211	ibid.
246	212	ibid.
247	213	ibid.
248	214	ibid.
249	215	ibid.
250	216	ibid.
251	217	ibid.
252	218	ibid.
253	219	ibid.
254	220	ibid.
255	221	ibid.
256	222	ibid.
257	223	ibid.
258	224	ibid.

In addition to changing the title and claims, amending the specification and submitting a new Abstract, Applicants are filing this Second Preliminary Amendment in order to address the issues raised in the October 4, 1994 Office Action issued in the parent application (Serial

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No. 08/046,004). By so doing at this juncture, Applicants and their attorney are hoping to narrow the substantive issues, if not to place the instant claims in allowable condition. The rest of this paper is directed to the October 4, 1994 Office Action.

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ISSUES FROM OCTOBER 4, 1994 OFFICE ACTION (S.N. 08/046,004)

A. Restriction Requirement & Election of Species

In the October 4, 1994 Office Action, the Examiner indicated, among other things, that the requirement set forth in the November 18, 1993 Office Action, "is still deemed proper and is therefore made FINAL."

In the event that any requirement for restriction or election of species is undertaken for this application (as it was in the parent), Applicants would respectfully incorporate their remarks presented in their June 23, 1994 Request for Reconsideration of Restriction Requirement and Election of Species Under 37 C.F.R. §1.143. Applicants would respectfully remind the Examiner further that restriction of the subject matter originally filed on June 23, 1982 as U.S. Patent Applications Serial No. 06/391,440, was already undertaken by the separate filing of eight divisional applications (two of which have already issued as U.S. patents; see Exhibits 2 and 3). In the two related and issued patents, U.S. Patent Nos. 5,328,824 and 5,260,433, no such restriction or election requirement was ever proposed during the prosecution. Finally, having just reached the "special" status as a "Five Year Case" [see Manual of Patent Examining Procedure (MPEP) §707.02(a)], it is respectfully submitted that the remaining issues are few in number and narrow in scope. By examining all of the instant claims together in what was originally a divisional application (and thus, already narrowed from the originally claimed subject matter), the Examiner will be expending the necessary effort to terminate its prosecution, as recommended in MPEP §707.02(a), *supra*.¹ Accordingly, it is urged that no restriction requirement or species election be implemented for the instant claims, such a requirement or election only serving to hinder any efforts to terminate the prosecution of the instant application.

¹ Applicants are mindful of the statutory provisions of 35 U.S.C. §121 with respect to restriction practice. In the circumstances at hand, however, it is believed that the failure to require election and species in the instant application would not be contrary to the statute because previous related applications have already been deemed to be free of any such requirements.
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B. Submission of Suppl. Information Disclosure Statement

In the October 4, 1994 Office Action, the Examiner indicated that the Information Disclosure Statement filed on 8/22/94 contains references which were not considered because no copy was furnished. In response, Applicants are submitting as exhibits to their concurrently filed Supplemental Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.97-1.98 a copy of each of the following twenty-three (23) references thought to be previously submitted with their August 22, 1994 IDS:

Torrence et al., J. Med. Chem. 21:228-231 (1978) [Exhibit 7 in
8/22/94 IDS]

Michelson, Biochem. Biophys. Acta 91:1-13 (1964) [Exhibit 8]

Cech et al., Nucleic Acids Research 2:2183-2192 (1979) [Exhibit 9]

Bleackley et al., Nucleic Acids Research 2:683-690 (1975) [Exhibit
11]

Roberts et al., J. Am. Chem. Soc. 74:668-669 (1952) [Exhibit 12]

Bauman et al., Chromosoma 84:1-18 (1982) [Exhibit 13]

Bauman et al., Exp. Cell Res. 128:485-490 (1980) [Exhibit 14]

Gerhard et al., Proc. Natl. Acad. Sci.(USA) 78:3755-3759 (1981)
[Exhibit 15]

Miller, J., "Experiment 52, Assay of the lac Repressor by Binding to
Operator," Experiments in Molecular Genetics, Cold Springs
Harbor Laboratory, pages 367-370 (1972) [Exhibit 16]

Ueda et al., Carbohydr., Nucleosides & Nucleotides 5:261-271 (1978)
[Exhibit 17]

Brunngraber et al., J. Biol. Chem. 242:4834-4840 (1967) [Exhibit 18]

Wilchek et al., Biochemistry 6:247-252 (1967) [Exhibit 19]

Monod et al., J. Mol. Biol. 12:88-118 (1965) [Exhibit 22]

Dean Engelhardt et al.
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Filed: June 7, 1995
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Pastan et al., Science 169:339-344 (1969) [Exhibit 23]

Gilbert et al., Proc. Natl. Acad. Sci.(USA) 70:3581-3584 (1973)
[Exhibit 24]

Carrico et al., UK Patent Application No. GB 2 040 943 A, published
September 3, 1980 [Exhibit 39]

Japanese Patent No. 57-42632, issued March 1986 [Exhibit 69]

Japanese Patent No. 61-103824, issued May 1986 [Exhibit 70]

Kourilsky et al., PCT Application No. WO 83/02276, published July 7,
1983 [Exhibit 87]

Scherberg, U.S. Patent No. 4,260,737, issued April 7, 1981
[Exhibit 90]

Salam et al., Carbohydrate Research 102:139-146 (1982) [Exhibit 95]

Kang, European Patent Application Publication No. 0 061 761 A1,
published October 6, 1982 [Exhibit 99]

and

Sela et al., German Patent Application No. DE-A-25-07-901,
published September 10, 1970 [Exhibit 100].

Applicants and their attorney would also like to point out that three
references cited in their August 22, 1994 IDS still remain unavailable.
These include:

Kropinski et al., Gen. Virol. 6:85 (1970) [Exhibit 4]

Bhat, Syn. Proc. in Nucleic Acid Chemistry 1:521 (1968) [Exhibit 6]

and

Caruthers, Second Annual Congress for Recombinant DNA Research,
Los Angeles, CA (1982) [Exhibit 27]

Applicants' attorney and his legal assistant are continuing their
efforts to locate these three above-named missing references. Their
efforts include requests through outside professional retrieval services.
As soon as any of the missing references is located, Applicants will
update their IDS submissions to include the now missing copy or copies.

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C. The Objection and Rejection Under 35 U.S.C. §112, 1st ¶

In the October 4, 1994 Office Action, the specification was objected to and claims 204-207, 209, 215, 216 and 225-227 were rejected because "the specification, as originally filed, allegedly did not provide support for the invention as is now claimed." In the Office Action (page 3), the Examiner stated:

... Support for claims 204-207, 209, 215, 216 and 225-227 was not pointed out nor was it found in the original disclosure. For example, claim 216, which depends ultimately from claim 204, recites a nucleotides(sic) wherein Sig comprises several enzymes. In the original disclosure, the claim reciting these enzymes, claim 197, was dependent from a very different claim base.

The objection and rejection are respectfully traversed.

In response, Applicants respectfully submit that the original disclosure does indeed provide support for the invention now claimed, and embraced by claims 204-224 and 227-258. With respect to claim 216 and its recitation of various enzymes as Markush members for Sig, Applicants concur with the Examiner's assessment that in the "original disclosure" [Serial No. 06/391,440, filed on June 23, 1982], the claim reciting these enzymes, claim 197, was dependent from a very different base claim." Applicants are quick to point out that the enzymic Markush members for Sig in claims 216 (and also 250 added above) include alkaline phosphatase, acid phosphatase, β -galactosidase, ribonuclease, glucose oxidase and peroxidase. All six of these named enzymes find support in the originally filed claims. The original claims are directed to the following specific enzymes: alkaline phosphatase (original claim 125), acid phosphatase (original claim 41), β -galactosidase (original claims 84 and 126), ribonuclease (original claim 129), glucose oxidase (original claim 127), and horseradish peroxidase (original claim 128).

It is well-recognized under the law that "original claims constitute their own description" and that "later added claims of similar scope and wording are described thereby." For support in the law for the latter, see, for example, *In re Koller*, 613 F.2d 819, 823-824, 204 USPQ 702, 706 (CCPA 1980). Thus, the enzyme recitation in the instant claims is clearly supported by the disclosure as it was originally filed. Basing support on originally filed claims is by no means the only way that later filed claims may be supported by the original disclosure. In this regard, Applicants

respectfully note that the instant specification also supports the enzymes named in the claims. See, for example, page 96, last paragraph, which refers to alkaline phosphatase, glucose oxidase, horseradish peroxidase and ribonuclease in the first sentence in the paragraph. It is believed that other support exists in the specification for the enzymes at hand.

Withdrawal of the previous objection and rejection under 35 U.S.C. §112, first paragraph, is respectfully urged.

D. The Rejection Under 35 U.S.C. §103

Claims 204-207, 209, 215, 216 and 225-227 were rejected in the October 4, 1994 Office Action under 35 U.S.C. §103 as being allegedly unpatentable over Kourilsky, GB 2 019 408, published October 31, 1979. In the Office Action, the Examiner stated:

Claim 204 is drawn to nucleotides having a phosphate moiety, a sugar moiety, a base and a "sig" moiety. Claims 205-207, 209, 215, 216 and 225-227 further limit claim 204 to recite a phosphate covalent bond, wherein Sig is at least three carbon atoms, and wherein Sig is an enzyme, for example β -galactosidase.

Kourilsky teaches a nucleotide, which contains phosphate, sugar and base moieties, which is chemically coupled to the enzyme β galactosidase (Kourilsky p. 2, lines 2-3 and 15). The claims differ from Kourilsky in the recitation of the phosphate linkage. However, Kourilsky teaches "It goes without saying that it is possible to resort to other chemical modifications of the probes . . . (p. 2, lines 44-46)," and "the chemical modification must be such that it does not prevent the possible subsequent hybridization of the probe with the DNA (p. 2, lines 15-16)." It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to couple the β galactosidase to the phosphate moiety for the expected benefit of freeing the base moiety for hybridization.

The obviousness rejection is respectfully traversed.

At the outset, it is respectfully submitted that *prima facie* obviousness cannot be established in this instance. As enunciated by the Court of Appeals for the Federal Circuit (CAFC) in In re Lalu and Foulleltier, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (1984):

In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. *In re Taborsky*, 502 F.2d 775, 780, 183 USPQ 50, 55 (CCPA 1974).;

The entire rejection seems to be predicated on the quoted statements in the cited Kourilsky document (page 2, lines 15-16 and 44-46), to wit, "It goes without saying that it is possible to resort to other chemical modifications of the probes" (lines 44-45), and that "the chemical modification must be such that it does not prevent the possible subsequent hybridization of the probe with the DNA" (lines 15-16).

To borrow Kourilsky's expression, it goes without saying that his "chemical modifications" do not even begin to touch the phosphate moiety as set forth in the instant claims. When Kourilsky speaks of chemical modifications, he does not even mention the components of a nucleotide, such as the phosphate moiety, sugar moiety or base moiety. More to the point, he states:

It goes without saying that it is possible to resort to other chemical modifications of the probe and, if necessary, of the enzyme, to effect their coupling, preferably after the hybridization reaction, and that it is possible to reverse the modifying agents of the probe and of the enzyme, respectively.

[page 2, lines 44-46]

In the subsequent paragraph, Kourilsky proceeds to expand on the "chemical modifications" alluded to in the passage quoted above. Specifically, he states in lines 47-52:

Other pairs of modifying agents of the probe on the one hand, and of the enzyme, on the other hand, may also be used. By way of example, the following pairs are mentioned, the first of these agents being preferably used for the chemical modification of the probe and the second for the chemical modification of the enzyme. For example, the probe may be modified, by a known method, by metallic ions (mercury for example) and the development is done by means of an enzyme having hydrosulphide groups (-SH), or coupled to a support including such groups.

Thus, Kourilsky "chemical modifications" are nothing more than modifications to the modifying agents - and **not** to the instant chemical modification involving the phosphate moiety.

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As far as the earlier reference in Kourilsky to "chemical modification" found on page 2, lines 16-17, that reference also falls far short of the teaching that is necessary to sustain *prima facie* obviousness. In those two lines, Kourilsky states:

It is self-evident that the chemical modification must be such that it does not prevent the possible subsequent hybridization of the probe with the DNA sequence or fragment sought.

Again, that reference to a "chemical modification" does not in any way refer to modifying the phosphate moiety of a nucleotide, particularly where the only explanation for "chemical modification" comes later in Kourilsky's disclosure where he speaks only to modifications in the modifying agents (page 2, lines 44-52), discussed *supra*.

In view of the foregoing remarks and established legal principles, Applicants respectfully urge that the previous obviousness rejection under 35 U.S.C. §103 be reconsidered before it is applied again to the instant claims.

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The fee for the newly added claims, 234-258 is \$506, based upon an excess number of twenty-three (23) claims presented above the thirty (30) claims already paid or authorized with the continuation request. The Patent and Trademark Office is hereby authorized to charge the amount of \$506 to Deposit Account No. 05-1135. The Patent and Trademark Office is further authorized hereby to charge Deposit Account No. 05-1135 for any other fees due in connection with this Preliminary Amendment or the accompanying Supplemental Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.97-1.98, or to credit any overpayment thereto.

Early and favorable action on the claims presented for examination is courteously solicited.

Respectfully submitted,

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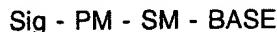
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**A PHOSPHATE-MOIETY LABELED NUCLEOTIDE, AND AN OLIGO- OR
POLYNUCLEOTIDE, AND OTHER COMPOSITIONS COMPRISING SUCH
PHOSPHATE-MOIETY LABELED NUCLEOTIDES**

Abstract of the Disclosure

The present invention provides a nucleotide having the formula,



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a pyrimidine, purine or 7-deazapurine moiety. PM is attached to the 3' or the 5' position of the sugar moiety when the nucleotide is a deoxyribonucleotide and at the 2', 3' or 5' position when the nucleotide is a ribonucleotide. BASE is attached to the 1' position of SM from the N¹ position when BASE is a pyrimidine or the N⁹ position when BASE is a purine or 7-deazapurine. Sig is covalently attached to PM directly or via a chemical linkage, and represents a detectable moiety covalently attached to SM directly or through a linkage group. Also provided are an oligo- or polynucleotide comprising at least one such phosphate-moiety labeled nucleotide, and other compositions including those wherein a polypeptide is terminally ligated or attached to the oligo- or polynucleotide. The phosphate-moiety labeled nucleotide, and the oligo- or polynucleotides and other compositions comprising such phosphate-moiety labeled nucleotides, are useful as diagnostic tools for detecting analytes and as therapeutic agents.